

Synthesis of amides using polyacrolein-based oximino dithiobenzoic anhydrides

K AISWARYA KUMARI and K SREEKUMAR*

Department of Chemistry, University of Kerala, Kariavattom Campus, Trivandrum 695 581, India

MS received 20 January 1994; revised 28 October 1994

Abstract. The use of polyacrolein-based oximino dithiobenzoic anhydrides in the synthesis of amides is illustrated. The reagent was prepared by polymer analogous reactions starting from 2% DVB crosslinked poly(acrolein-styrene)terpolymer. It was found to selectively acylate amines and amino acids to give the corresponding amides and peptides. The new acyl transfer reagent possessed the desired characteristics of polymeric reagents, including operational simplicity, filterability and regenerability. The influence of solvent, temperature, duration of reaction and molar excess of the reagent in these acylation reactions were studied to find out the optimum conditions.

Keywords. Polyacrolein oximino dithiobenzoic anhydrides; polymer analogous reaction; polymeric acyl transfer reagents.

1. Introduction

A polymeric organic reagent can provide an effective alternative to its low molecular weight counterpart if its design is such that it allows easier isolation of the desired product after the reaction, and if the polymeric byproduct can be regenerated and recycled for further use. A number of reactive species have been attached to polymeric supports based on this idea and have been successfully used in organic synthesis (Hodge and Sherrington 1980; Kraus and Patchornik 1980; Mathur *et al* 1980; Akelah and Sherrington 1981; Sreekumar and Pillai 1987; George and Pillai 1988; Devaky and Pillai 1990). It has been established that the nature of the polymeric support matrix has a significant role in the extent of swelling and hence on the course of the reactions with soluble substrates (Crowley and Rapoport 1976; Grieg and Sherrington 1978; Sket *et al* 1984; Sreekumar and Pillai 1989). The polarity of the support material is one of the most important factors influencing the reactivity of the bound species with the substrate (Patchornik 1982; George and Pillai 1990). Here, an attempt has been made to prepare a new class of acyl transfer reagents based on styrene-acrolein-DVB terpolymer as the support matrix. The introduction of acrolein repeating units into crosslinked polystyrene matrix is expected to give better flexibility and hydrophilicity.

This paper describes the preparation and the synthetic application of polyacrolein based oximino dithiobenzoic anhydride resins. This reagent is used for the preparative level conversion of amines to amides.

*For correspondence

2. Experimental

2.1 General

Solvents used were reagent grade and were purified according to literature procedures. Microanalyses were performed at the Regional Sophisticated Instrumentation Centre, Indian Institute of Technology, Madras. Melting points were determined on a hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 397 spectrometer using KBr pellets. Thin layer chromatography was performed on pre-coated silica gel plates.

2.2 Styrene-acrolein-DVB terpolymer

The monomers were washed with sodium hydroxide solution (1%, 3 times) and with water (3 times) to remove the inhibitor. Poly(vinyl pyrrolidone) (150 mg) was dissolved in water (100 ml) and heated to 80–90°C. The mixture of monomers, say, styrene (16.78 ml), acrolein (1.11 ml) and DVB (0.95 ml) (for 2% crosslinked resin) and azobisisobutyronitrile (200 mg) as initiator were added to the hot solution with vigorous stirring. The mixture was heated at 90°C with stirring for 12 h. The precipitated polymer was filtered, washed with water, carbon tetrachloride, benzene, ethanol and methanol (15 ml × 2 times each) and dried at 60°C. Yield 14.5 g, IR (KBr): 1700 cm⁻¹ (C=O str), 2720 cm⁻¹ (C–H str).

2.3 Preparation of polyacrolein oximes

The acrolein terpolymer (10 g) was mixed with hydroxylamine hydrochloride (25 g) and pyridine (30 ml) in chloroform (50 ml). The mixture was refluxed at 80°C for 20 h. The resin was filtered and was washed successively with chloroform, water, ethanol and methanol (20 ml × 3 times each). The resin was then dried in vacuum to constant weight. Yield, 11 g. IR (KBr): 3340 cm⁻¹ (O–H str), 1650 cm⁻¹ (C=N str), 2720 cm⁻¹ (C–H str), % N, 5.6.

2.4 Preparation of polyacrolein based oximino dithiocarbonate resin

The polyacrolein oxime resin (10 g) was added to a five-fold molar excess of an equimolar mixture of CS₂ (16 ml, 200 mmol) and NaOH (10 g, 200 mmol). The mixture was shaken for 10 h at room temperature. The resin was collected by filtration and washed with water, ethanol and methanol (25 ml × 1 min × 5 times each), and dried in vacuum to afford the dithiocarbonate resin. Yield, 11.6 g. IR (KBr): 1650 cm⁻¹ (C=N str), 1040 cm⁻¹ (C=S str), 950 cm⁻¹ (N–O str), 650 cm⁻¹ (C–S str), 2720 cm⁻¹ (C–H str). %N, 5.4; %S, 4.1.

2.5 Preparation of polyacrolein based oximino dithiobenzoic anhydride resin

The polyacrolein based oximino dithiocarbonate resin (10 g) was suspended in a mixture of acetonitrile and chloroform (1:1 v/v, 50 ml) and pyridine (5 ml). A 3-fold molar excess of benzoyl chloride was added to the suspension and the mixture was stirred for 8 h. The reaction mixture was filtered to collect the resin, washed with acetonitrile, water, ethanol and methanol (20 ml × 2 min × 3 times each), and dried in vacuum. Yield, 12.5 g. IR (KBr): 1650 cm⁻¹ (C=N str), 1040 cm⁻¹ (C=S str), 1730 cm⁻¹ (C=O str), 950 cm⁻¹ (N–O str), 650 cm⁻¹ (C–S str), 2720 cm⁻¹ (C–H str). %N, 4.2; %S, 3.8.

2.6 Estimation of acyl group capacity

The polymeric acylating agent (1 mmol, calculated from the sulphur content) was suspended in chloroform (20 ml) along with aniline (0.5 mmol) and was shaken for 2 h when maximum conversion was noticed as judged by tlc. The reaction mixture was filtered and washed with chloroform. The excess aniline present in the filtrate was extracted with 2N HCl, made up to 250 ml and estimated by iodometric titration. The capacity obtained was 2.43 meq/g.

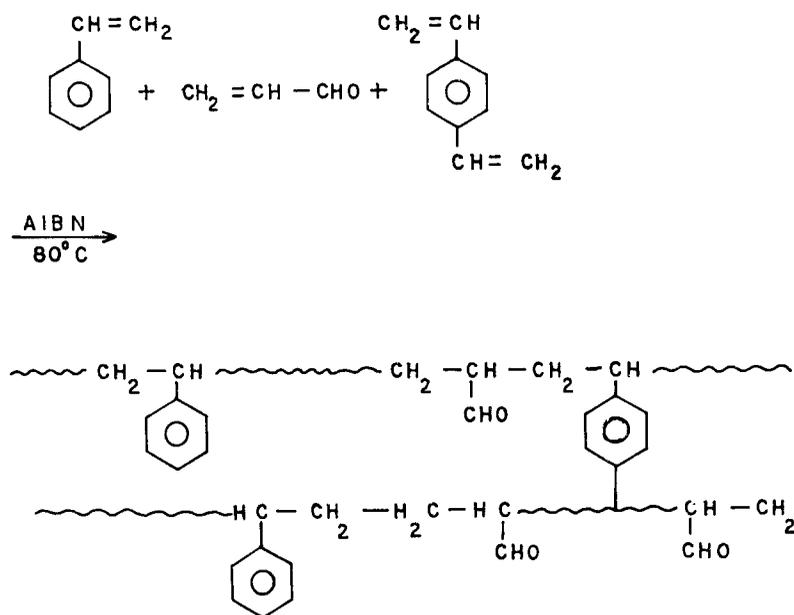
2.7 Acylation of amines using polyacrolein based oximino dithiobenzoic anhydride resin

A suspension of the polyacrolein based oximino dithiobenzoic anhydride resin (1 mmol), amine (0.5 mmol) and chloroform (20 ml) was shaken for a definite time, when maximum conversion was obtained as indicated by tlc. The mixture was filtered and washed with chloroform (10 ml \times 3 times). The filtrate together with the washings was collected, washed with HCl (1:1, 20 ml) to remove any unreacted amine, followed by washing with water, and dried over anhydrous CaCl_2 . Evaporation of the solvent afforded the amide.

3. Results and discussion

3.1 Preparation and characterization of polyacrolein based oximino dithiobenzoic anhydride resin

Terpolymers of acrolein and styrene with DVB were prepared by suspension polymerization, and were used as the macromolecular support (scheme 1). This support is



Scheme 1. Preparation of styrene-acrolein-DVB terpolymer.

residue afforded the amide. Using the oximino dithiobenzoic anhydride resin, a number of amines were acylated. Details are given in table 1. In cases where complete conversion of the amine was not possible, before evaporation of the filtrate, the excess amine was extracted with dil. HCl. The products were characterized by comparison with authentic samples (IR and melting point).

Polyacrolein oximino dithiobenzoic anhydride resin is selective for acylating an amino group in the presence of a hydroxyl group or carboxyl group. The resin did not react with ethyl alcohol to give ethyl benzoate, on prolonged reaction with *o*-aminophenol it produced only *o*-hydroxy benzanilide and with glycine gave only benzoyl glycine as the product.

Acylation of aniline gave 78% yield whereas *o*-toluidine gave 84% yield. *p*-Toluidine and *p*-chloroaniline gave 80% and 70% of the respective anilides. The higher extent of acylation of toluidines may be due to their higher nucleophilicity compared to aniline. The converse is true for the chloroanilines. Aliphatic amines like methyl amine also give higher yields of the amide.

3.3 Reaction conditions and extent of acyl transfer

The acylation reaction using polyacrolein oximino dithiobenzoic anhydride resin was found to be affected by the nature of the solvent, temperature and the effective concentration of the reagent function. It has been observed that only when there is an effective interaction between the reagent function attached to the macromolecular matrix, the substrate and the reaction medium, reaction takes place with reasonable extent of functional group conversion.

3.3a *Effect of solvent*: The systematic investigation of the effect of solvent on the acylation of amines using polyacrolein-based oximino dithiobenzoic anhydride resin reveals that chloroform is the most effective solvent. The acylation reaction was carried out in solvents of varying polarity. The solvents used were dichloromethane, chloroform, carbon tetrachloride, acetonitrile and dioxane. Solvents which are capable of swelling the polymer network and which are also able to dissolve the low molecular substrates are found to be suitable for carrying out the acylation reactions. Percentage conversion after a specified period was noted and the results obtained are given in table 2.

Table 1. Acyl transfer reactions using polyacrolein oximino dithiobenzoic anhydride resin.

Amine	Solvent	Duration ^a (h)	Yield (%)
Aniline	CHCl ₃	2-0	78
<i>o</i> -Toluidine	CHCl ₃	2-0	84
<i>m</i> -Toluidine	CHCl ₃	2-0	70
<i>p</i> -Toluidine	CHCl ₃	2-0	80
<i>m</i> -Chloro aniline	CHCl ₃	2-0	68
<i>p</i> -Chloro aniline	CHCl ₃	2-0	70
<i>o</i> -Amino phenol	CHCl ₃	2-0	75
Glycine	Dioxane: water (1:1)	2-5	68
Methyl amine	Dioxane	2-5	82

^aIndicates time for maximum conversion

Table 2. Effect of solvents on acylation of aniline using polyacrolein oximino dithiobenzoic anhydride resin^a.

Acylation reagent	% Yield of anilide formed in				
	CH ₂ Cl ₂	CHCl ₃	CCl ₄	CH ₃ CN	Dioxane
Polyacrolein oximino dithiobenzoic anhydride resin	60	78	72	70	82

^aSubstrate to resin ratio, 1:2; temperature, 30°C; time, 3 h

Table 3. Effect of temperature on acylation of aniline using polyacrolein oximino dithiobenzoic anhydride resin^a.

Acylation reagent	% Yield of anilide formed at (°C)				
	20°	30°	40°	50°	60°
Polyacrolein oximino dithiobenzoic anhydride resin	68	78	76	72	72

^aSubstrate to resin ratio, 1:2; solvent, chloroform; time, 3 h

Polar solvents like acetonitrile and dioxane have a pronounced effect on the extent of acylation of aniline. Percentage conversion was around 80–85%. The reagent is so swollen in dioxane that the work-up of the reaction mixture itself is difficult. Chloroform also gives reasonable amounts of benzanilide from aniline on acyl transfer. The work-up of the reaction mixture is comparatively easy with chloroform as the solvent, since it swells the polymer only to a reasonable extent. Thus for the polyacrolein-based oximino dithiobenzoic anhydride resin, chloroform is found to be the best solvent.

3.3b Effect of temperature: In order to study the effect of temperature on the reactivity of polyacrolein oximino dithiobenzoic anhydride resin, acylation of aniline was conducted at various temperatures in chloroform as the solvent. The percentage conversion obtained after a definite period of time was noted and the results are given in table 3.

As the temperature is increased, the yield of anilide obtained sharply increased up to room temperature (30°C) and then it gradually decreased on further increase in temperature indicating that the acyl group transfer could possibly be reversible at higher temperature.

3.3c Effect of duration of reaction: The percentage yield of the anilide obtained was determined at fixed time intervals using polyacrolein oximino dithiobenzoic anhydride resin. The results are given in table 4.

The yield of anilide was found to increase progressively up to a time when the maximum yield was obtained. After that the percentage yield was found to decrease slightly. The slight decrease in the yield of the isolated product on prolonged reaction was found to be due to some extent of physical adsorption of the amide on the crosslinked polymer.

Table 4. Acylation of aniline using polyacrolein oximino dithiobenzoic anhydride resin at various time intervals^a.

Acylation reagent	% Conversion after (h)					
	0.5	1	1.5	2	2.5	3
Polyacrolein oximino dithiobenzoic anhydride resin	42	56	68	78	78	75

^a Substrate to resin ratio, 1:2; solvent, chloroform; temperature, 30°C

Table 5. Acylation of aniline using polyacrolein oximino dithiobenzoic anhydride resin with different resin to amine ratios^a.

Acylation reagent	% Conversion when the molar ratio is				
	1:1	2:1	3:1	4:1	5:1
Polyacrolein oximino dithiobenzoic anhydride resin	50	78	80	82	83

^a Solvent, chloroform; temperature, 30°C; Time, 3 h

Table 6. Regeneration of polyacrolein oximino dithiobenzoic anhydride resin.

No. of cycles	Benzoyl group capacity (meq/g)	Isolated yield (%)
1	2.43	78
2	2.43	78
3	2.38	75
4	2.35	73

^a Acylation of aniline in chloroform at room temperature; Yield noted after 3 h; aniline to resin ratio, 1:2

3.3d Effect of molar ratio on the extent of acylation: Acylation of aniline was carried out by varying the molar excess of polyacrolein oximino dithiobenzoic anhydride resin, the other experimental conditions being the same. The acylation reaction of 0.5 mmol of aniline with different molar excess of the polymeric reagent was studied. In the present study, the relative concentrations investigated were 1:1, 2:1, 3:1, 4:1 and 5:1. When molar equivalents were used, the reaction did not go to completion in any case, irrespective of the duration of the reaction. The details of the acylation reaction are presented in table 5.

With increase in resin to amine ratio, there was a corresponding increase in the percentage yield of the anilide formed.

3.4 Recyclability of the polyacrolein oximino dithiobenzoic anhydride resin

The spent resin from the acylation step was treated with an equimolar mixture of carbon disulphide and sodium dithiocarbonate resin which on subsequent benzylation gave the original oximino dithiobenzoic anhydride resin. The extent of acylation using this resin was found to be only slightly decreased even after several repeated recycling processes. The change in the capacity of the resin and the percentage of acylation in the course of the recyclization steps are presented in table 6.

The foregoing studies indicate that the polyacrolein based oximino dithiobenzoic anhydride resin can be used as a solid phase reagent for the acylation of amines to amides. These functionalized resins retained their bead form characteristics, and they possessed the desired conditionalities of a polymeric reagent, including operational simplicity, filterability and regenerability.

Acknowledgement

The authors thank the University Grants Commission, New Delhi for a fellowship to K.A.

References

- Akelah A and Sherrington D C 1981 *Chem. Rev.* **81** 557
Crowley J I and Rapoport H 1976 *Acc. Chem. Res.* **9** 135
Greig J A and Sherrington D C 1978 *Polymer* **19** 163
Devaky K S and Pillai V N R 1990 *Proc. Indian Acad. Sci. (Chem. Sci.)* **102** 521
George B K and Pillai V N R 1988 *Macromolecules* **21** 1867
George B K and Pillai V N R 1990 *J. Polym. Sci. A28* 2585
Hodge P and Sherrington D C (eds) 1980 *Polymer-supported reactions in organic synthesis* (New York: Wiley)
Kraus M A and Patchornik A 1980 *Macromol. Rev.* **15** 55
Mathur N K, Narang C K and Williams R E 1980 *Polymers as aids in organic chemistry* (New York: Academic Press)
Mathew G D and Pillai V N R 1993 *Proc. 5th Kerala Science Congress* p. 336
Patchornik A 1982 *Macromolecules* (eds) H Benoit and P Rempp (Oxford: Pergamon) p. 113
Sket B, Zupan M and Zuppet P 1984 *Tetrahedron* **40** 1606
Sreekumar K and Pillai V N R 1987 *Polymer* **28** 1599
Sreekumar K and Pillai V N R 1989 *Macromolecules* **22** 3303
Vogel A I 1989 *Textbook of practical organic chemistry* 5th edn. (London: ELBS/Longman) p. 1259